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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,646	02/10/2006	Alan David Borthwick	PG5041USW	5114

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EXAMINER	
GRAZIER, NYEEMAH	
ART UNIT	PAPER NUMBER
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,646	BORTHWICK ET AL.	
	Examiner	Art Unit	
	Nyeemah Grazier	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,10 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-6,8,10 and 11* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/6/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

FIRST ACTION ON THE MERITS

I. ACTION SUMMARY

Claims 1-6, 8, 10, 11 are currently pending.

II. PRIORITY

This application is a 371 of PCT/EP03/13799, filed on December 4, 2003 and claims benefit under 35 U.S.C. §119 (a-d) to United Kingdom 0228552.6, filed on December 6, 2002.

III. INFORMATION DISCLOSURE STATEMENT

The information disclosure statement (IDS) submitted on June 6, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

IV. REJECTION(S)

CLAIM REJECTIONS - 35 USC § 112, SECOND PARAGRAPH

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 11 is drawn to a process of manufacturing comprising reacting a compound of formula (II) with a compound of formula (III). Formula (III)is a sulfonyl group having a substituent "T." The substituent "T" is not described in the claim.

CLAIM REJECTIONS - 35 USC § 112, FIRST PARAGRAPH

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the claim attempts to claim more that what is enabled in the disclosure. Namely, the invention seeks protection over any and all conditions "susceptible to amelioration by a thrombin inhibitor" using the compound of claim 1. Thus, in its broadest interpretation, the claim reads on methods for treating neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease; and treatment of tumors.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The relevant factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph have been set forth in *In re* Wands. See *In re* Wands, 8 USPQ.2d 1400 (1988). The factors are as follows:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

For clarity, the analysis of 112, first paragraph will be separated into each factor.

The Nature of the Invention

The invention is drawn to treating a patient suffering from a condition susceptible to amelioration by a thrombin inhibitor using the compounds and pharmaceutical

compositions of Formula (I). Thrombin inhibitors have vast functions. For example, the inhibitors may have utility as anti-coagulant agents, as agents for the treatment of tumors, and treatment of neurodegenerative diseases such as Alzheimer's disease. Currently, there are no known agents that treat Alzheimer's and neurodegenerative diseases all inclusively.

The Level of Skill in the Art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity. The central characteristic of Alzheimer's disease is the deficiency in the level of the neurotransmitter Acetylcholine, which plays an important role in memory. Alzheimer's disease, for example, is an extraordinary disease to treat and has been subjected to a vast amount of research. Despite an enormous number of different approaches, the skill level in the art is so low relative to the difficulty of task that the only success has come from treatment by compounds such as Acetylcholinesterase inhibitors (e.g. Aricept®, Cognex®, Exelon®, and Reminyl®).

The Predictability or Lack Thereof in the Art

Because of high level of unpredictability associated with treatment of a tumor or treatment of Alzheimer's disease, a greater amount of evidentiary support is needed to satisfy the requirement of 35 U.S.C 112, first paragraph. The pharmacology requires screening in vitro and in vivo studies to determine and identify a specific compound that show the desired pharmacological efficacy and the mechanism thereof. There is no predictability of how compounds antagonize receptors. Furthermore, it is also unpredictable because there are thrombin inhibitors that are more selective than others. It is noted that the pharmaceutical art is unpredictable and requires the embodiments to be individually assessed for physiological activity. Thus, the more unpredictable the art,

more information in support of the invention is required to satisfy the statute. See In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970).

The Amount of Direction or Guidance Present

The applicant has not demonstrated sufficient guidance to provide a skilled artisan with sufficient guidance to practice the invention. Further, the applicant discloses that an effective amount of the compound will be administered without providing any direction other than the compounds of the invention. The therapeutic index of a drug in humans is almost never known and is only determined through clinical trials.

The Presence or Absence of Working Examples

The specification fails to bridge the gap between the compounds inhibitory effects as a thrombin inhibitor and the effects of the compound when administered to a host to treat different therapeutic areas, such as transient ischemic attacks and Alzheimer's disease. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that compounds fall within the scope of a claim will posses the alleged activity. See *In re* Riat (CCPA 1964) 327 F2d 685, 140USPQ 471; *In re* Barr (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

The Breadth of the Claims

The breadth of the claim may be interpreted to include any and all diseases associate with thrombin inhibition. Thus, the claim may include unrelated classes of diseases such as neurodegenerative diseases (Parkinson's disease and Alzheimer's disease) and cardiovascular diseases (Stroke, coronary thrombosis) and immunological diseases (treatment of tumors).

The Quantity of Experimentation Needed

Based on the unpredictable nature of the invention and the state of the prior art and the breadth of the claims, one of ordinary skill in the art would be burdened with undue

"experimentation study" to determine whether the claimed compounds would prevent diseases that are unrelated etymologically. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ.2d 1001 (stating that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable"). Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which compounds would *prevent*, for example, allergic diseases by the method encompassed in the instant claims, with no assurance of success.

In sum, to overcome this rejection the Examiner suggests that Applicant insert the diseases in the claim and list only the related diseases supported in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

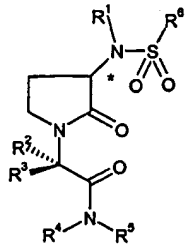
Graham v. John Deere Co. set forth the factual inquiries necessary to determine obviousness under 35 U.S.C. §103(a). *See Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Specifically, the analysis must employ the following factual inquiries:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

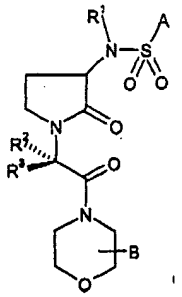
Claims 1-6, 8, 10 and 11 are rejected because the invention is rendered obvious over WO 02/100830 A1 (Glaxo Group Ltd.).

The instant invention is drawn to compounds, compositions, method of making, and method of using the compounds of Formula (I).

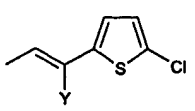


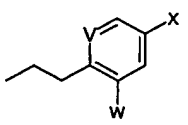
The Scope and Content of the Prior Art (MPEP §2141.01)

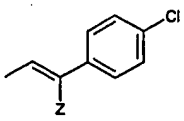
The WO 02/100830 A1 publication teaches the compounds of formula (I), compositions of formula (I) and the method of making and using the products of formula (I) as Factor Xa inhibitors.



The instant invention and the inventions disclosed in the WIPO publications mentioned above disclose comparable core structures. The only difference is that in the instant invention R6 represents, inter alia, alkenylene-chlorothienyl alkylene-phenyl (optionally substituted) and alkenylene-chlorophenyl. See below.

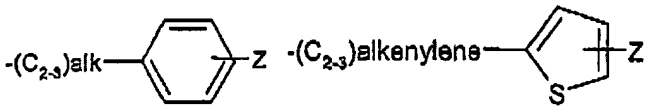






Wherein the substituent "Y" represents CH3, CF3; V may represent CH; W may represent H, methyl, chloro or fluoro; X may represent chloro, bromo, fluoro or methyl; Z methyl or fluoro; and Z may represent methyl or fluoro.

Substitution R6 is the equivalent of "A" in the WO 02/100830 publication, wherein "A" may represent C2-3alkenylene-phenyl (substituted by Z) and C2-3 alkenylene-thienyl (substituted by Z). See, WO 02/100830 at 3, ll. 10-15. See below.



Wherein Z represents one or two optional substituents independently selected from halogen and hydroxyl. Id. at p. 3, l. 12.

The Difference Between the Prior Art and the Claims (MPEP §2141.02)

There is no substantial difference between the instant invention and the invention disclosed in the publication. The only difference is in scope. The instant invention and the invention in the publication are drawn to identical core. (Note that R4 and R5 together with the nitrogen atom form a morpholine ring). Variable "A" which is equivalent to variable "R6" in the instant invention, is a little broader in scope as it is drawn to C2-3alkenylene-phenyl (substituted by Z) and C2-3 alkenylene-thienyl (substituted by Z) which reads on the instant invention. Applicant is the lexicographer. As such alkenyl has been defined as straight or branched and therefore C3 alkenylene would include –CH=C(CH3)-. See WO 02/100830 at 10, ll. 22-25. Additionally, "Z" on the phenyl or thienyl may represent halogen. The instant invention is chloro substituted.

Alternatively, it is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. *In re* Woods, 582 F.2d 638, 199 USPQ 137 (CCPA 1978).

Resolving Level of Ordinary Skill in the Pertinent Art

The pertinent art is cardiovascular drug discovery and generally medicinal chemistry. One of ordinary skill in the pertinent art of medicinal chemistry, specifically, cardiovascular drug discovery would have the motivation to make and use to instant invention because there is motivation to make in the instant compounds in the abovementioned references which teach compounds useful for Factor Xa. The motivation to make claimed compound derives from the expectation that structurally similar compounds are generally expected to have similar properties and have similar utilities. In re Gyurik, 596 F. 2d 1012, 201 USPQ 552 (CCPA 1979).

Prima Facie Obviousness-The Rational and Motivation (MPEP §2142-2413)

It is well established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in light of the admitted knowledge in the art, to a person of ordinary skill in the art. In re Boe, 148 USPQ 507 (CCPA 1966). For an invention to be obvious, two things must be found in the prior art: 1) the suggestion of the invention, and 2) the expectation of success. In re Vaeck, 20 USPQ.2d 1438, 1441 (Fed. Cir. 1991).

The prima facie case for obviousness is derived from the preferred teaching of the references. The reference teaches preferred compounds and preferred variable substituents in the "Detailed Description of the Invention." The preferred compounds of the publication include 4-[(2S)-2-[(3S)-3-[[[(1E)-2-(5-chloro-2-thienyl)ethenyl]sulfonyl]amino]-2-oxo-1-pyrrolidinyl]-1-oxopropyl]-morpholine and 4-[(2S)-2-[(3S)-3-[[[(1E)-2-(4-chlorophenyl) ethenyl]sulfonyl]amino]-2-oxo-1-pyrrolidinyl]-1-oxopropyl]-morpholine. Furthermore the publication teaches how to make the compound of the instant invention. See, WO 02/100830 at p. 29-30.

Thus, although the claims are not identical, the prior art of reference suggests the instant invention.

Obviousness-Type Double Patenting

- Claims 1-6, and 8 are rejected over claims 1-9 of U.S. Patent No. 7,186,717 B2.
- Claims 1-6 and 8 are provisionally rejected over claim 1 of co-pending application 10/537,645.
- Claims 10 is provisionally rejected over claim 1 of copending application 11/548,402.
- Claim 11 is provisionally rejected over claim 3 of copending application 11/548,404.
- Claims 1-6 and 8 are provisionally rejected over claims 1-7 and 9 of copending application 11/548,395.
- Claims 1-6 and 8, 10 and 11 are provisionally rejected over claims 1-9, 12, 14 and 15 of copending application 11/378,947.
- Claims 1- 6, 8, 10 and 11 are provisionally rejected over claims 1-9, 12, 14 and 15 of copending application 11/384,094.

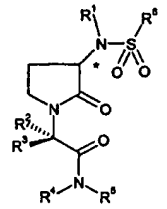
A rejection based on nonstatutory double patenting is based on a judicially created doctrine grounded in public policy so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re* Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re* Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re* Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re* Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re* Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). See also M.P.E.P. § 804 (2001).

Obvious-type nonstatutory double patenting rejection is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. §103" with the distinction that the double patent rejection is not considered prior art. Id. See also In re Braithwaite, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Thus, the analysis employed in an obviousness-type double

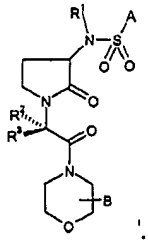
patent rejection is consistent with a §103(a) analysis set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966).

(1) Claims 1-6, and 8 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent 7,186,717 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant invention in claim 1-6 and 8 is drawn to compounds and pharmaceutical compositions of formula (I).

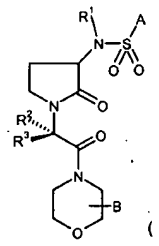


The conflicting patent claims are drawn to the compounds and compositions of formula (I)

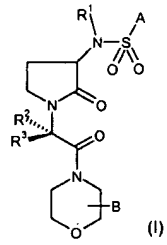


(2) Claims 1-6 and 8 are provisionally rejected over claim 1 of co-pending application 10/537,645 wherein the conflicting claims are drawn to compounds (E)-2-(5-Chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide.

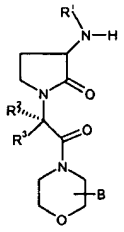
(3) Claims 10 is provisionally rejected over claim 1 of copending application 11/548,402 wherein the conflicting claim is drawn to a method of treating a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor comprising administering a therapeutically effective amount of the compound of formula (I).



(4) Claim 11 is provisionally rejected over claim 3 of copending application 11/548,404 wherein the conflicting claim is drawn to the method of preparing the compound of formula (I) comprising the reacting formula (XVI) with formula (VIII).



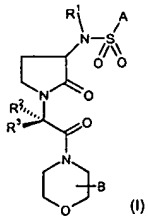
(I)



(XVI)

(VIII)

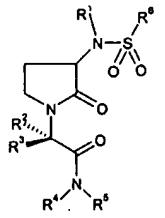
(5) Claims 1-6 and 8 are provisionally rejected over claims 1-7 and 9 of copending application 11/548,395 wherein the conflicting claims are drawn to compounds and pharmaceutical compositions of formula (I).



(I)

(6) Claims 1-6 and 8, 10 and 11 are provisionally rejected over claims 1-9, 12, 14 and 15 of copending application 11/378,947 and claims 1- 6, 8, 10 and 11 are provisionally rejected over claims 1-9, 12, 14 and 15 of copending application 11/384,094 wherein the

copending applications are drawn to compounds, compositions and methods of making and using the compounds of formula ((Ic).



(Ic)

Determining the Scope and Contents of the 7,186,717 B2 and the Co-pending Application

- Claims 1-6, and 8 are rejected over claims 1-9 of U.S. Patent No. 7,186,717 B2.

There is no substantial difference between the instant invention and the invention disclosed in the publication. The only difference is in scope. The instant invention and the invention in the publication are drawn to identical core. (Note that R4 and R5 together with the nitrogen atom form a morpholine ring). Variable "A" which is equivalent to variable "R6" in the instant invention, is a little broader in scope as it is drawn to C2-3alkenylene-phenyl (substituted by Z) and C2-3 alkenylene-thienyl (substituted by Z) which reads on the instant invention. Applicant is the lexicographer. As such alkenyl has been defined as straight or branched and therefore C3 alkenylene would include –CH=C(CH3)-. See WO 02/100830 at 10, ll. 22-25. Additionally, "Z" on the phenyl or thienyl may represent halogen. The instant invention is chloro substituted.

Alternatively, it is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. *In re* Woods, 582 F.2d 638, 199 USPQ 137 (CCPA 1978).

- Claims 1-6 and 8 are provisionally rejected over claim 1 of co-pending application 10/537,645.

The difference between the instant invention and the invention in the copending application is that the copending application is drawn to a species of formula (I). Thus, the difference is in scope.

- Claims 10 is provisionally rejected over claim 1 of copending application 11/548,402.

The instant invention and the copending claim are both drawn to the same method of use. The only difference is in the scope of formula (I). There is no substantial difference between the instant invention and the invention disclosed in the publication. The only difference is in scope. The instant invention and the invention in the publication are drawn to identical core. (Note that R4 and R5 together with the nitrogen atom form a morpholine ring). Variable "A" which is equivalent to variable "R6" in the instant invention, is a little broader in scope as it is drawn to C2-3alkenylene-phenyl (substituted by Z) and C2-3 alkenylene-thienyl (substituted by Z) which reads on the instant invention. Applicant is the lexicographer. As such alkenyl has been defined as straight or branched and therefore C3 alkenylene would include –CH=C(CH3)-. See WO 02/100830 at 10, ll. 22-25. Additionally, "Z" on the phenyl or thienyl may represent halogen. The instant invention is chloro substituted.

Alternatively, it is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. *In re* Woods, 582 F.2d 638, 199 USPQ 137 (CCPA 1978).

- Claim 11 is provisionally rejected over claim 3 of copending application 11/548,404.

The instant invention and the copending claim are both drawn to the same method of manufacturing. The only difference is in the scope of formula (I). There is no substantial difference between the instant invention and the invention disclosed in the publication. The only difference is in scope. The instant invention and the invention in the publication are drawn to identical core. (Note that R4 and R5 together with the nitrogen atom form a morpholine ring). Variable "A" which is equivalent to variable "R6" in the instant invention, is a little broader in scope as it is drawn to C2-3alkenylene-phenyl (substituted by Z) and C2-3 alkenylene-thienyl (substituted by Z) which reads on the instant

invention. Applicant is the lexicographer. As such alkenyl has been defined as straight or branched and therefore C3 alkenylene would include –CH=C(CH3)-. See WO 02/100830 at 10, ll. 22-25. Additionally, "Z" on the phenyl or thienyl may represent halogen. The instant invention is chloro substituted.

Alternatively, it is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. *In re* Woods, 582 F.2d 638, 199 USPQ 137 (CCPA 1978).

- Claims 1-6 and 8 are provisionally rejected over claims 1-7 and 9 of copending application 11/548,395.

There is no substantial difference between the instant invention and the invention disclosed in the publication. The only difference is in scope. The instant invention and the invention in the publication are drawn to identical core. (Note that R4 and R5 together with the nitrogen atom form a morpholine ring). Variable "A" which is equivalent to variable "R6" in the instant invention, is a little broader in scope as it is drawn to C2-3alkenylene-phenyl (substituted by Z) and C2-3 alkenylene-thienyl (substituted by Z) which reads on the instant invention. Applicant is the lexicographer. As such alkenyl has been defined as straight or branched and therefore C3 alkenylene would include –CH=C(CH3)-. See WO 02/100830 at 10, ll. 22-25. Additionally, "Z" on the phenyl or thienyl may represent halogen. The instant invention is chloro substituted.

Alternatively, it is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. *In re* Woods, 582 F.2d 638, 199 USPQ 137 (CCPA 1978).

- Claims 1-6 and 8, 10 and 11 are provisionally rejected over claims 1-9, 12, 14 and 15 of copending applications 11/378,947 and 11/384,094.

There is no substantial difference between the instant invention and the invention disclosed in the publication. The only difference is in scope. The instant invention and the invention in the publication are drawn to identical core. (Note that R4 and R5 together with the nitrogen atom form a morpholine ring). Variable "R6" which is equivalent to variable "R6" in the instant invention, is a little broader in scope as it is drawn to –Z-Rh wherein Z represents C1-3alkylene or –C2-3alkenylene and wherein Rh represents phenyl or a 5 or 6 membered heterocyclic group with at least one heteroatom selected from O, N, or S.

It is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. *In re* Woods, 582 F.2d 638, 199 USPQ 137 (CCPA 1978).

Ascertaining the Differences Between the Patent, the Copending Application and the Instant Claims

The difference is in scope as mentioned above. Also, the substitution of a hydrogen atom for a methyl is an obvious variant where it is the only difference in the compound. See In re Wood, Whittaker, Sterling, and Ohta, 199 USPQ 137 (CCPA 1978)

Resolving Level of Ordinary Skill in the Pertinent Art

The pertinent art is cardiovascular drug discovery and generally medicinal chemistry. One of ordinary skill in the pertinent art of medicinal chemistry, specifically, cardiovascular drug discovery would have the motivation to make and use to instant invention because there is motivation to make in the instant compounds in the abovementioned references which teach compounds useful for Factor Xa. The motivation to make claimed compound derives from the expectation that structurally similar compounds are generally expected to have similar properties and have similar utilities. In re Gyurik, 596 F. 2d 1012, 201 USPQ 552 (CCPA 1979).

Prima Facie Obviousness-The Rational and Motivation (MPEP §2142-2413)

The prima facie case for obviousness is derived from the preferred teaching of the references. The reference teaches preferred compounds and preferred variable substituents. In the "Best Mode section of the patent application. Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application.

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

V. OBJECTION(S)

Claims must end with a period. Claim 5 is objected to because there is not a period at the end of the claim.

VI. CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nyeemah Grazier whose telephone number is (571) 272-8781. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:30 a.m. - 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached on (571) 272 - 0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Very truly yours,

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